Oxford University Hospitals NHS
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myeLOma bOne MrI Study

The development and pilot testing of a new Magnetic Resonance (MR) imaging protocol to quantify both myeloma disease burden and associated bone loss

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No potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

1. SYNOPSIS

Study Title	The development and pilot testing of a new Magnetic Resonance (MR) imaging protocol to quantify both myeloma disease burden and associated bone loss	
Internal ref. no. / short title	LOOMIS- myeLOma bOne MrI Study	
Study Design	Observational Prospective Cohort	
Study Participants	Group 1- Myeloma Group 2- Monoclonal Gammopathy of Uncertain Significance (MGUS) Group 3- Healthy Volunteers	
Planned Sample Size	60 Group 1- Myeloma- 34 Group 2- MGUS - 13 Group 3 - Healthy Volunteers - 13	
Planned Study Period	September 2017 – December 2021	
	Objectives	**Outcome Measures**
Primary	To develop and pilot test a novel Magnetic Resonance (MR) imaging protocol with the aim to accurately: **1. Quantify tumour burden** **2. Quantify bone loss**	**Novel imaging based endpoints:** 1. DW-MRI (Diffusion Weighted-Magnetic Resonance Imaging): ADC (apparent diffusion coefficient) change (Pawlyn *et al*, 2016) 2. Total spinal 'hole' volume 3. Total spine 'collapse' volume 4. FSA (Fine Structural Analysis): trabecular wall thickness (Rafferty *et al*, 2016) **Correlate endpoints:** • Bone density (DXA imaging) • Serum CTX-1 • Serum P1NP • Further experimental serum biomarkers of myeloma bone disease
Secondary	To pilot test a novel MR imaging protocol with the aim to accurately: **1. Detect longitudinal changes in tumour load with therapy** **2. Detect longitudinal changes in bone microarchitecture with therapy** **3. Assess participants Quality of Life (EQ-5D) throughout the study**	1 and 2 - Repeat quantification of endpoint parameters after induction therapy and best response achieved by IWMG criteria or at treatment failure

	4. Assess participants experience of the novel MR imaging scan	3 – Analyse participants quality of life using data from the EQ-5D-5L questionnaire 4- Analyse participants experience of the novel MR imaging using data from MRI/DXA scanning questionnaire

2. ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
CI	Chief Investigator
CRF	Case Report Form
DWI	Diffusion Weighted Imaging
DWMRI	Diffusion Weighted Magnetic Resonance Imaging
DXA	Dual-energy X-ray Absorptiometry
FSA	Fine Structure Analysis
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMWG	International Myeloma Working Group
MGUS	Monoclonal Gammopathy Of Uncertain Significance
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NOC	Nuffield Orthopaedic Centre
NRES	National Research Ethics Service
PET-CT	Positron Emission Tomography-Computed Tomography
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee

SOP	Standard Operating Procedure
SRE	Skeletal Related Events
WBLDCT	Whole-body low dose Computed Tomography
sFLC	Serum free light chains

3. BACKGROUND AND RATIONALE

Multiple myeloma, a malignancy of monoclonal B-cells, is the second most common haematological malignancy, compromising of 2% of all cancers in the UK and is currently incurable. At diagnosis and each relapse, treatment of myeloma consists of conventional chemotherapy combined with novel agents. In those fit enough, autologous (and in some cases allogeneic) stem cell transplantation is used to prolong remissions (NICE, 2016). A number of tests are used for disease quantification to guide therapy; however these tests each have limiting factors. Bone marrow histology using a bone marrow biopsy is painful and invasive; it also cannot predict global myeloma infiltration, which is not uniform and varies through the skeleton, and no bone loss information can be obtained. Serum paraprotein, light or heavy chain quantification must be used for regular monitoring; however this fails in non-paraprotein secreting myelomas, and although it tracks the secretory capacity of a plasma cell clone, that feature can change over the course of the disease.

PET-CT (positron emission tomography- computed tomography) is the imaging gold standard in myeloma for quantifying total disease burden (Cavo *et al*, 2017). This cannot however quantify bone loss, either microarchitecture changes or lytic lesions. It therefore cannot be used to track response to anti-bone-resorptive therapies.

There are a number of widely used modalities that are currently available to visualise bone destruction; including conventional MR (magnetic resonance), whole body low dose CT (WBLDCT) (Pianko *et al*, 2014) and X-ray skeletal survey. However, none of these techniques are quantitative (Marti-Bonmati *et al*, 2015). Of particular note, high-resolution bone volume quantifying CT techniques cannot be used on the central skeleton due to high radiation exposure; although trialled on cortical bone in the peripheral skeleton (Farr *et al*, 2013), this is not the usual site of myeloma bone loss. DXA (Dual-energy X-ray Absorptiometry) scans are widely used in the UK for assessing bone density in patients with osteoporosis but are an insensitive tool in myeloma as it does not show fractures (Marti-Bonmati *et al*, 2015), and therefore are not routinely commissioned for imaging myeloma patients. All of these imaging modalities require significant time and resource commitment over a typical myeloma disease course. Typically a patient may require X rays, PET-CT and spinal MRI within a few weeks for complete staging. If there were a single imaging method that could provide all required quantified staging information this would have both economic and patient convenience benefits.

The use of Magnetic Resonance Imaging (MRI) in Multiple Myeloma has increased dramatically over the last 10 years (Derlin & Bannas, 2014). MRI offers improved detection of lesions in the spine, pelvis, sternum, skull and scapulae as well as exceptional depiction of the spinal cord and nerve roots, detection of soft tissue manifestations and the ability to differentiate between physiological and myeloma-infiltrated bone marrow. Several studies have shown that asymptomatic patients with detectable lesions on MRI have a higher probability to become symptomatic earlier than patients without such lesions. This has therefore been incorporated in the revised IMWG diagnostic criteria (Rajkumar *et al*, 2014).

In addition to morphological MRI, there are newer functional MR techniques such as diffusion-weighted imaging (DWI). However there is limited published data for DWI (Diffusion Weighted Imaging) in the context of initial staging. A recent study has shown that diffusion-weighted imaging not only allows for detection of myeloma manifestations such as lytic lesions (DW-MRI was found superior to the whole-body x-ray for the detection of bone involvement in 20 patients with relapsed, refractory myeloma in all

areas of the skeleton except the skull), but also that the DWMRI-generated apparent diffusion coefficient (ADC) significantly differs before and after initiation of therapy, so allowing calculation of change in disease burden (Giles *et al*, 2015). DW-MRI uses ADC measurement to quantify disease and is influenced by tissue microarchitecture. The speed, quantitative capabilities and superior sensitivity compared with conventional MRI sequences have led to the adoption of DW-MRI at several leading myeloma centres worldwide. ADC measurements are not without challenges, as they can be influenced by scanner manufacturer and field strength, however are perceived to be less susceptible to equipment and physiological influences than PET-CT. In a recent trial (Pawlyn *et al*, 2016), DW-MRI scans were compared with FDG (f-fluorodeoxyglucose) PET-CT and found to detect a statistically significant higher burden of myeloma disease. Investigations into the patient experience of DW-MRI have suggested that the DW-MR imaging technique is acceptable to patients as 86% found the overall experience acceptable. It is therefore proposed to be a novel non-ionising radiation imaging modality for quantitative assessment of disease burden and therapy response (Latifoltojar *et al*, 2017; Pawlyn *et al*, 2016). Importantly however, DW MRI cannot measure bone density.

The extent of lytic bone disease, the major cause of morbidity in myeloma affecting over 90% of patients, still cannot be quantified. Lytic lesions as seen on X-rays take many years to heal. In MGUS (Monoclonal gammopathy of uncertain significance); a precursor of multiple myeloma without any signs of the malignant disease (Bauerle *et al*, 2009); it is suspected that early bone destruction is associated with transformation to malignancy, but no appropriate imaging modality exists to assess or monitor this, meaning this patient cohort may be missing out on disease modifying therapies. We wish to address this important unmet clinical need by piloting a novel MR imaging assessment of disease burden and bone loss in myeloma. Farr et al using peripheral qCT have shown MGUS patients have early bone loss (Farr *et al*, 2013). This has been subsequently termed as monoclonal gammopthay of skeletal significance, MGSS (Drake, 2014).

On to the state of the art DW-MRI technique of quantifying disease burden, we propose to add 2 further experimental MR components to quantify myeloma bone loss, which can take the form of a) lytic lesions (holes), b) vertebral collapse and c) trabecular thinning. We will address this in the following way:

1. High resolution 3D imaging of spine and pelvis: 'hole' and 'collapse' volumes will be quantified. This is entirely novel and will be produced by OCMR scientists.

2. Fine SA: Osteotronix' ***fine***SA® (FSA) technology is able to extract microstructural information from MRI data sets acquired on a standard clinical MRI scanner. In this study, we are particularly interested in using the FineSA metric as a correlate of trabecular wall thickness, to indicate bone remodelling. The FSA metric has been shown to correlate tightly with gold standard bone density measurements in rats (Evans *et al*, 2014) and human cadaveric spine specimens (Rafferty *et al*, 2016). The only other means to measure these parameters is by computed tomography, not feasible in the human body in vivo due to the high radiation dose that would result from microstructural CT of central bones. FSA will be performed at two sites in the lumbar spine, and repeated on each patient (within the same appointment) to assess reproducibility. Further central skeleton sites may be added with technique development.

We therefore aim to develop and pilot a MR imaging protocol and assess its ability to achieve the following: quantification of tumour burden and bone loss, detecting longitudinal changes in tumour load

with therapy and detecting longitudinal changes in microarchitecture with therapy. We also aim to investigate sensitivity of the different imaging techniques in detection of bone loss. This will be investigated by correlating the DXA imaging data (accepted imaging for measuring longitudinal changes in bone density) with our experimental protocol, to see if it is possible to achieve quantifiable data of bone density.

We hypothesize that this imaging tool will be superior to the combined current standard-of-care investigations in the quantification of tumour burden and bone loss. There are currently no tools available for quantifying structural changes to bone and overall bone loss in myeloma.
To our knowledge, this has never been done before; if shown to be feasible, such a method would have two important applications: to precisely guide commissioned therapies in the clinic, so improving patient management; and as an exciting, novel research tool for the longitudinal combined assessment of tumour burden and cancer-induced bone disease in response to therapy.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

	Objectives	**Outcome Measures**
Primary	To develop and pilot test a novel MR imaging protocol with the aim to accurately: **1. Quantify tumour burden** **2. Quantify bone loss**	**Novel imaging based endpoints:** 1. DW-MRI: ADC change (Pawlyn *et al*, 2016) 2. Total spinal 'hole' volume 3. Total spine 'collapse' volume 4. FSA: trabecular wall thickness (Rafferty *et al*, 2016) **Correlate endpoints:** • Bone density (DXA imaging) • Serum CTX-1 • Serum P1NP • Further experimental serum biomarkers of myeloma bone disease
Secondary	To pilot test a novel MR imaging protocol with the aim to accurately: **1. Detect longitudinal changes in tumour load with therapy** **2. Detect longitudinal changes in bone**	1 and 2 - Repeat quantification of endpoint parameters after induction therapy and best response achieved by IWMG criteria or at treatment failure

	microarchitecture with therapy **3. Assess participants Quality of Life (EQ-5D) throughout the study** **4. Assess participants experience of the novel MR imaging scan**	3 – Analyse participants quality of life using data from the EQ-5D-5L questionnaire 4- Analyse participants experience of the novel MR imaging using data from MRI/DXA scanning questionnaire

5. STUDY DESIGN

This novel MR protocol is developing new metrics and combining elements that have not previously been combined therefore, there will be a protocol development phase prior to trial recruitment in which a group of healthy volunteers will be scanned to ensure timings and data collection is optimized. This phase will take place prior to trial start and is not included as part of this protocol, as it is already covered by REC approval for OCMR protocol development.

Once the protocol development phase has been completed, 60 subjects will be recruited to take part in this study; Group 1: Myeloma, (n=34), Group 2: MGUS, (n=13) and Group 3: Healthy age-matched volunteers, (n=13). Participants from Groups 1 and 2 will be identified and approached by a healthcare professional in the oncology clinic at the Churchill Hospital, Oxford. Group 3 participants will usually be the partners of the participants from group 1 and 2, and they will be recruited alongside the participants in Groups 1 and 2.

As participants in Groups 1 and 2 will be recruited at the point of either diagnosis or relapse, any standard investigations their clinician deems necessary for their diagnostic evaluation within NHS protocols will also be performed. Following recruitment, all participants (Groups 1-3) will undergo the first study appointment, the experimental combined MR imaging protocol. Alongside this, participants in Groups 1 and 2 only will undergo the DXA imaging scan and the bone biomarker blood and urine tests. Once both imaging appointments have been completed, all participants will be asked to complete a short questionnaire relating to the MRI imaging and Groups 1 and 2 will be asked to complete this questionnaire for the DXA imaging too; no questionnaires are to be completed for the bone biomarker test. Groups 1 and 2 participants will also be asked to complete a validated quality of life questionnaire.

Participants in Groups 1 and 2 will undergo a further experimental MR scan, DXA imaging and bone biomarker blood tests at 6 months or at time of progression/relapse, whichever is sooner (but no sooner than 3 months after the initial investigations) to evaluate change in disease burden and bone loss. The reason participants in Group 2 will be rescanned at 6 months even if they have not progressed to myeloma and are not on therapy, is to address the following questions, 1. Can trabecular thinning progression be detected with time in MGUS patients whose paraprotein is stable or rising? 2. Reproducibility test: In

patients with a stable paraprotein, if assumed that trabecular thickness is stable or at most slightly worse over 6 months, is trabecular quantification reproducible over time?

In addition to this, all participants in Groups 1 and 2 will also be asked to complete the short questionnaire relating to the MRI and DXA imaging and the quality of life questionnaire for assessment of patient experiences of both imaging procedures, both at the first study appointment and at the 6 month follow up appointment. Standard of care clinical investigations will be repeated within NHS protocols if clinically indicated. Results of relevant NHS diagnostic investigations, clinical outcomes and survival data will be collected and stored.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Patients with newly diagnosed or relapsed myeloma, smouldering myeloma (Group 1; n=34), MGUS (intermediate or high risk) (Group 2; n= 13), and healthy age-matched volunteers (Group 3; n=13) are eligible to be included in the trial if they meet the following criteria:

6.2. Inclusion Criteria

Inclusion Criteria (All Groups)

- Participant is able to and willing give informed consent for participation in the study.
- Male or Female, aged 18 years or above.

Inclusion Criteria (Groups 1 and 2)

- Newly diagnosed myeloma or newly- relapsed myeloma eligible for next therapy,
- Smouldering myeloma or intermediate or high risk MGUS
- Patients attending Oxford NHS Haematology-oncology centre
- Diagnoses of MGUS, Smouldering Myeloma and MM- made in accordance with the clinical diagnostic criteria set forth by IMWG (International Myeloma Working Group)

6.3. Exclusion Criteria

Exclusion Criteria (All Groups)

- Those who are unable or unwilling to give informed consent

- Women who may be pregnant, breast feeding or women of child-bearing potential who are unwilling or unable to take sufficient precautionary measures will be excluded due to DXA imaging.

Exclusion Criteria (Groups 1 and 2)

- Signs of Spinal Cord Compression
- Patients with documented metastatic lesions from another type of malignancy
- Known contraindication for a MRI scan (see Appendix B: contraindications to MR scan), including unacceptable pain on lying flat for 1 hour.

7. STUDY PROCEDURES

Summary: In order to pilot test a novel MRI imaging protocol, this study will compare current, NHS-available myeloma tumour and bone disease assessment tools, with the novel MR imaging technique. Blood sampling for bone turnover biomarkers, DXA imaging and the novel MR scan will be performed in addition to any standard NHS tests deemed necessary by clinical care team. Three groups of participants will be included, Group 1 (Myeloma), Group 2 (MGUS) and Group 3 (Healthy Volunteers). Group 3 will only receive a single MR scan with no further investigations whereas Groups 1 and 2 will go onto receive DXA scan and blood tests. Relevant baseline information including medical history, prior course of disease and use of bone modifying therapy will be recorded at start of study for Groups 1 and 2, and once more at 6 months post-recruitment, or at relapse/progression if sooner.

7.1. Recruitment

Newly diagnosed or newly relapsed myeloma patients (Group 1) with or without X-ray detectable bone disease, Smouldering myeloma and high or intermediate MGUS patients (Group 2), without X-ray detectable bone disease, will be invited to participate. Healthy age-matched volunteers (Group 3) will be recruited from the local myeloma support group community, (for example patients' partners).

Patients will be identified by the clinician or clinical care team. Potential patients will then be approached by the myeloma clinical research team during a routine clinic visit and given information about the study. If the participant is interested then they will have a further detailed discussion about the study with a research coordinator and will be given the participant information sheet to take home. They will return to clinic after a minimum period of 24 hours, and will have the opportunity to ask any questions regarding the study. If the participant remains happy to enter the study, their informed consent will be obtained by the investigator prior to initiating any study related investigations.

We anticipate a 10% screen failure for group 1 participants, primarily due to pain and contraindications for MRI. We anticipate 5% screen failure rate for group 2 participants due to contraindications for MRI scan. Both of these figures have been incorporated in the sample size calculations.

7.2. Informed Consent

Informed consent will be taken at a routine clinic visit. The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Copies of the Participant Information Sheet and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. A member of the clinical team will talk through the PIS with the participant before Informed Consent is obtained.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

Those who have not communicated a decision regarding consent may be re-approached on one occasion after 2 months by the local research team.

7.3. Screening and Eligibility Assessment

7.3.1 Screening Logs

The research team will be expected to maintain a screening log of all potential participants. Participants will not be registered at consent and therefore during screening, potential participants should be identified by limited information only; this should include initials, date of birth, screening date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility if known, or refused to participate). Screening logs will be filed in the trial master file.

7.3.2 Screening Assessments

All screening study assessments must be completed before any study procedures are carried out.

The following assessments will be carried out in order to establish eligibility for the study for participants in Groups 1 and 2 only.

- Medical History

Detailed history of myeloma/MGUS including; date of diagnosis, staging (International Staging System) and location(s) of bone disease as per standard of care should be recorded. Detailed description of all prior and ongoing diseases and disorders should be documented along with any myeloma or bone strengthening therapies that were received.

Particular Details on history of fractures, history of osteoporosis, bone pain and analgesia requirements should be documented. Details on use of radiotherapy or vertebral augmentation should be collected.

- Treatment History and Concomitant Medication(s)
  Details of treatment history and current concomitant medication including all medications, treatments and therapies used in the prior 4 weeks, as well as those currently being taken should be recorded.

- Physical Examination
  Physical examination including assessment of ECOG status (Group 1 only), height and weight should be recorded for all participants.

- Local Clinical Laboratory Evaluations
  - Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance
  - Immunology: Beta-2 microglobulin, paraprotein, quantitative immunoglobulins, serum free light chains
  - Haematology: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes
  - Bone marrow assessment (only Myeloma and Smouldering myeloma): bone marrow aspirate and trephine to confirm diagnosis of myeloma
  - Urine pregnancy test: for women of child bearing potential (WCP)

Participants in Group 3 will undergo the following screening assessments before any study procedures are carried out:

- Medical History
  Detailed history of any relevant previous medical conditions and their treatments
- Physical Examination
  Physical examination of height and weight to be recorded

7.3.3 Recruitment Logs

Participants deemed eligible after screening will be registered on to the study and be given a unique Study ID. Registered participants will be recorded on an enrolment log with information including Study ID, Date of Birth, Initials and hospital number as well as date of consent. No personal information, which may identify the participant, should be included on the recruitment log.

7.3.4 Participant Trial Card

After a participant has been enrolled onto the study, the research staff should inform the participant of their Study ID and provide a completed Participant Trial Card including details of dates of the scans and staff contact details.

7.4. Baseline Assessments

7. 4.1 Baseline Assessments for Groups 1 and Group 2

Once consent has been given, the first study appointment will be offered, within four weeks. This first study visit will include the MR imaging protocol, DXA scanning, bone biomarker blood/urine tests and completion of both questionnaires. These procedures are described in further detail below. An administrator will manage these attendance arrangements; however, participants will be required to make arrangements for transportation to and from the OCMR and NOC. Participants will be given the opportunity to claim back the travel expenses and details of how to do this is available in the Participant Information Sheet. Whenever possible, the administrator will try and arrange for the MRI and DXA scan to happen on the same day, should this not be possible and the scans are arranged for different days, the participants will have to attend an additional study visit.

1. Blood and urine samples for bone turnover biomarkers total ALP, PINP and serum CTX1 (Vasikaran *et al*, 2011). This will require a morning fasted 20ml clotted (serum) blood sample to be taken. Additional experimental assays of biomarkers for myeloma bone disease will be performed on these samples at the Oxford University Hospitals NHS Foundation trust laboratory. This assessment will take approximately 10 minutes.

2. Body composition using whole body DXA (1 hour radiology appointment at the NOC (Nuffield Orthopaedic Centre)). Bone Mineral Density (BMD) will be measured by (DXA) using a study approved densitometer. BMD measurements will be made at the lumbar spine (L1-4), hip, whole body and an Instant Vertebral Assessment (IVA). If participants have already had a DXA scan at one of these sites within 2 months of the visit date, then that scan will be used and the scan will not be repeated for that site. This assessment will take approximately 50 minutes.

3. Experimental MR imaging protocol (1 hour radiology appointment). MRI scans will be performed in a 60-minute protocol on the 1.5T or 3T Avanto MRI scanner (Siemens, Germany) installed at OCMR (Oxford Centre for Magnetic Resonance), John Radcliffe Hospital, Headington, Oxford, OX3 9DU. Scans will include: localizer images, high-resolution 3D imaging of the pelvis and lumbar spine, diffusion-weighted MRI imaging following the method described for use in myeloma patients by Giles *et al* (Giles *et al*, 2015; Giles *et al*, 2014; Pawlyn *et al*, 2016), and an experimental bone density quantification MR method based on published techniques (Evans *et al*, 2014; Rafferty *et al*, 2016), using software from Osteotronix Ltd, in the pelvis and two sites in the lumbar spine. Blinded data gathered from experimental MRs will be used to generate disease burden in percentage marrow infiltration, high-resolution 3D imaging-generated total spinal lytic and collapse volumes, and bone structure quantification. Marrow infiltration will be correlated with marrow infiltration data as determined by bone marrow biopsy (and PET-CT scans where performed). MR-generated bone density quantification and total spinal lytic and collapse volumes will be correlated with bone mineral density as estimated by DXA scan. As there is no

accepted “gold standard” method for quantifying myeloma-associated bone loss against which to compare, in all the healthy volunteers and in 10 myeloma patients who are tolerating the procedure without problem and who are willing repeat MR bone density measurements will be performed (a subsection of the whole protocol, lasting max. 15 minutes) within each attendance, to assess reproducibility.

4. At the end of both the experimental MR and the DXA scan, all participants will be asked to complete the Quality of Life Questionnaire and the novel MR experience questionnaire. This assessment will take approximately 15 minutes.

   See Appendix A for time frame of assessments.

No contrast medium will be used.

7.4.2 Baseline Assessments for Group 3 (Healthy Volunteer)

All baseline assessments for Group 3 will be the same as those for Groups 1 and 2 with the exception of Number 1 and 2. Healthy volunteers will not be required to give any (blood/urine) samples or have the DXA imaging.

If the MRI and DXA scans are on the same day for Groups 1 and 2, then the baseline visit will last for approximately 2.5 to 3 hours. However, if the MRI and DXA scans are on different days, then the baseline visit will last for approximately 1.5 to 2 hours and the DXA scan for approximately 1 hour. The baseline visit for Group 3 will last approximately 1.5 to 2 hours.

7.5. Subsequent Visits

For Groups 1 and 2, a follow up visit will take place 6 months after the baseline assessment.

Tests 1, 2, 3 and 4 from baseline assessment will be repeated in exactly the same way for both Group 1 and 2.

Repeat data collection (on intervening treatment and disease monitoring results, from hospital records) will be performed.

No subsequent data collection or assessment will be performed on Group 3 (Healthy volunteers) at 6 months, as the only purpose of their inclusion is to establish reproducibility and a normal range for experimental MR output data. Therefore, group 3 participation stops at the end of their baseline assessments.

7.6. Sample Handling

All participants will be assigned a unique study ID which will also be used to identify samples. All laboratory samples, will be anonymised to the research team for this study however, direct clinical care team will have access to identifiable information in order to create a report for clinical purposes to inform participants care.

Blood and urine samples for bone turnover biomarkers total ALP, PINP and serum CTX1 will be taken at baseline and follow up at 6 months for Groups 1 and 2; no samples will be obtained from participants in Group 3. This will require a morning fasted 20ml clotted (serum) blood sample to be taken. Additional experimental assays of biomarkers for myeloma bone disease will be performed on these samples at the Oxford University Hospitals NHS Foundation trust laboratory. All samples collected from Groups 1 and 2 at both baseline and follow up will be stored for the duration of the study to run analytes in parallel to limit batch wise processing. Samples collected for this study will not be stored for use in other research and will be destroyed after analysis. These samples will only be accessible to study staff and authorised personnel.

7.7. Discontinuation/Withdrawal from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

For participants who are withdrawn from the study, identifiable data or tissue already collected with valid consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. All withdrawal information including reason for withdrawal will be recorded on the Withdrawal CRF.

Every effort will be made to replace participants who have been withdrawn from the study.

7.8. Definition of End of Study

The ending of the study is the date of the final MR imaging assessment of the last participant.

8. INTERVENTIONS (IF APPLICABLE)

8.1 DW-MR imaging scans

MRI scans will be performed in a 60-minute protocol on the 1.5T Avanto MRI scanner (Siemens, Germany) installed at OCMR. Scans will include: localizer images, high-resolution 3D imaging of the pelvis and lumbar spine, diffusion-weighted MRI imaging following the method described for use in myeloma patients by Giles *et al* (Giles *et al*, 2015; Giles *et al*, 2014; Pawlyn *et al*, 2016), and an experimental bone density quantification MR method based on published techniques (Evans *et al*, 2014; Rafferty *et al*, 2016), using software from Osteotronix Ltd, in the pelvis and two sites in the lumbar spine.

8.2 DXA scans

DXA scans will be performed in a 1 hour protocol on the DXA scanner installed at the NOC. Scans will include: body composition, bone mineral density measured at the Lumbar spine (L1-4), hip, whole body and Instant Vertebral Assessment.

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

9.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see IRAS/NRES/HRA website).

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

The primary outcome of this study is the ADC in patients with and without a complete/very good partial response to therapy at follow-up. It is estimated that for group 1, between baseline and follow-up, 85% of individuals will reduce their myeloma burden from 40% to 10% or less compared with 15% who will achieve a partial response (a ratio of 0.15).

A previous study in a similar population the median ADC score improved from 0.79 (IQR 0.66 to 1.26) to 1.5 (IQR 0.88 to 1.83) in those with a complete/very good partial response compared with 0.66 (IQR 0.52 to 0.87) to 0.75 (0.51 to 1.27) in those with a partial response [Latifoltojar BJH 2016].

To detect a similar difference in this cohort with an ADC in complete/ very good partial response of 1.5 at follow-up vs. 0.75 in those with a partial response, a conservative estimated SD of 0.5, and a ratio of 0.15 will require 34 individuals in total (29 vs. 5) with 80% power and 0.05 type I error. We will, therefore, aim to recruit a total of 37 (31 vs. 6) participants for the study to allow for a dropout rate of 5%.

10.2. Analysis of Outcome Measures/Endpoints

Differences in baseline characteristics between participants groups (1, 2 and 3) will be compared using chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables.

To assess ability of MRI to detect improvement or deterioration in tumour burden and bone health, differences between DW-MRI data imaging from the two time-points (baseline and 6 months follow up) will be tested using paired t test. In addition, ADC, total spine 'hole' and 'collapse' volume and FSA trabecular wall thickness will be compared with bone mineral density at the lumbar spine, total hip and femoral neck T score and g/cm^2, serum CTX-1 and PINP using correlation analysis in group 1 (complete/very good partial response vs. partial response) and in group 2. These models will be run at baseline and at follow-up.

Differences between groups 1 and 2 in experimental MR measurements at follow up will be estimated using one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) when baseline values and potential confounders (including gender, age and body mass index (BMI)) are adjusted. Endpoints will be checked for normality and transformed if possible.

In order to determine the change in EQ-5D throughout the study, repeated measured linear regression analysis will be used where EQ-5D at baseline and follow up will be included as outcome and group as exposure.

Finally, a descriptive analysis of the novel MR imaging scan questionnaire will be conducted to understand participant's experience with the new technique.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Only authorised personnel involved in the clinical care of the patient will be able to access medical records and personal information for the purposes of the study or to inform clinical care. For confidentiality purposes, all participant information outside of clinical use will be anonymised with unique Study ID used to identify the patient. The research data will be stored and backed up using data protection structures within the Oxford University Hospitals NHS Foundation Trust (Sponsor) and University of Oxford. External collaborators will only be able to access anonymised patient data.

We will use password protection, ensuring computers cannot be accessed by people outside of the research unit, separating patient identifiers from clinical/research data and restricting access to who is able to link these two sets of data to the investigators on the study team. Electronic transfer of anonymised data will only use encrypted data.

11.2. Data Recording and Record Keeping

All essential documentation (CRFs) and research records will be stored in the Haematology Department administration offices, Churchill Hospital of Oxford University Hospitals NHS FT, in accordance with the applicable regulatory requirements with access to stored information restricted to authorized personnel only. All questionnaire and source document data will be entered on to a study database at the Oxford site. All electronic documentation and information will be kept on secured servers and computers in secured office areas. All documents will be version controlled. Essential documents will be archived as soon as practicable after the last patient entered onto the study has had their last study visit. All archived documents will be stored for 5 years in a secure location, and remain under access control of the CI, sponsor and regulatory authorities with an audit trail when material is retrieved.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2. ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the Good Clinical Practice.

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study will be run according to ICH GCP after review by the relevant ethics committee. The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID on all study documents and electronic database, with the exception of the CRFs where initials and DOB may be added. Documents with participant's identifiable information on will be filed and stored securely in locked filing cabinets in the Late Phase Haematology Department, Churchill Hospital; these will only be accessible to authorised personnel. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

All participants will be entitled to claim up to a maximum amount of £40 for travel expenses at the end of their participation in the trial. They will be required to fill out the travel expense form and hand this in along with the receipt to study staff. Once the claim has been processed, the payment will be made to the participants' account via the trust finance office.

13.7. Other Ethical Considerations

Any clinically significant incidental findings during testing of blood samples or during the scanning procedures (both MRI and DXA) will be reported to the CI and the CI will then report these to the patient and GP.

DXA:

DXA imaging entails a small exposure to radiation, equivalent of up to 21 days of background radiation for the duration of the study. The results of the lumbar spine, hip and vertebral fracture assessment will be made available to the patient's cancer care team for further clinical management. The Whole body

DXA will not routinely be reported on. Any incidental findings will be reported to the CI and the CI will then report these to the patient and GP.

MRI scan:

MRI safety checklist review will be conducted before admission into the scanner. Scan will last up to 60 minutes. Patients will be given sufficient non-sedating pain relief prior to the scan if required, and positioning will be optimised according to any potential chronic bone pain. If a patient finds lying in the scanner too uncomfortable despite pain relief, the procedure will be abandoned. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). No contrast injections will be given during the scan.

Blood sample collection:

Patient's skin will be prepped with an anti-septic wipe, which very rarely can cause a skin reaction. If a patient knows they are allergic to the anti-septic prep, another sterile agent will be used. They will then feel a sharp scratch as the needle is inserted and blood is drawn up into the sample bottles. It is exceedingly rare for blood tests to be complicated; however bleeding and infection are potential risks that will be minimised as much as possible by monitoring for bleeding after the test, and using sterile equipment and the sterile non-touch technique. All procedures will be carried out by appropriately trained healthcare professionals.

14. FINANCE AND INSURANCE

14.1. Funding

This study is partly funded by: Oxford NIHR Biomedical Research Centre. Amgen provides funding towards biomarkers, DXA and research MR scans.

14.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by

the Oxford NIHR Biomedical Research Centre and Amgen. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

16. REFERENCES

1.Bauerle, T, Hillengass, J, Fechtner, K, Zechmann, CM, Grenacher, L, Moehler, TM *et al* (2009) Multiple myeloma and monoclonal gammopathy of undetermined significance: importance of whole-body versus spinal MR imaging. *Radiology,* **252,** 477-485.

2.Cavo, M, Terpos, E, Nanni, C, Moreau, P, Lentzsch, S, Zweegman, S *et al* (2017) Role of ¹⁸F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group. *The Lancet Oncology,* **18,** e206-e217.

3.Derlin, T, Bannas, P (2014) Imaging of multiple myeloma: Current concepts. *World J Orthop,* **5,** 272-282.

4.Drake, MT (2014) unveiling skeletal fragility in patients diagnosed with MGUS: no longer a condition of undetermined significance? *J Bone Miner Res,* **29,** 2529-2533.

5.Evans, BAJ, James, TW, James, K, Cox, A, Farr, L, Paisey, SJ *et al* (2014) Preclinical Assessment of a New Magnetic Resonance-based Technique for Determining Bone Quality by Characterization of Trabecular Microarchitecture. *Calcified Tissue International,* **95,** 506-520.

6.Farr, JN, Zhang, W, Kumar, SK, Jacques, RM, Ng, AC, McCready, LK *et al* (2013) Altered cortical microarchitecture in patients with monoclonal gammopathy of undetermined significance. *Blood,* **123,** 647-649.

7.Giles, SL, deSouza, NM, Collins, DJ, Morgan, VA, West, S, Davies, FE *et al* (2015) Assessing myeloma bone disease with whole-body diffusion-weighted imaging: comparison with x-ray skeletal survey by region and relationship with laboratory estimates of disease burden. *Clinical Radiology,* **70,** 614-621.

8.Giles, SL, Messiou, C, Collins, DJ, Morgan, VA, Simpkin, CJ, West, S *et al* (2014) Whole-Body Diffusion-weighted MR Imaging for Assessment of Treatment Response in Myeloma. *Radiology,* **271,** 785-794.

9.Latifoltojar, A, Hall-Craggs, M, Rabin, N, Popat, R, Bainbridge, A, Dikaios, N *et al* (2017) Whole body magnetic resonance imaging in newly diagnosed multiple myeloma: early changes in lesional signal fat fraction predict disease response. *Br J Haematol,* **176,** 222-233.

10.Marti-Bonmati, L, Ramirez-Fuentes, C, Alberich-Bayarri, A, Ruiz-Llorca, C (2015) State-of-the-art of bone marrow imaging in multiple myeloma. *Curr Opin Oncol,* **27,** 540-550.

11.NICE (2016) Myeloma: diagnosis and management. NICE guideline [NG35]. https://http://www.nice.org.uk/guidance/ng35 *Accessed* February 2016

12.Pawlyn, C, Fowkes, L, Otero, S, Jones, JR, Boyd, KD, Davies, FE *et al* (2016) Whole-body diffusion-weighted MRI: a new gold standard for assessing disease burden in patients with multiple myeloma? *Leukemia,* **30,** 1446-1448.

13.Pianko, MJ, Terpos, E, Roodman, GD, Divgi, CR, Zweegman, S, Hillengass, J *et al* (2014) Whole-Body Low-Dose Computed Tomography and Advanced Imaging Techniques for Multiple Myeloma Bone Disease. *Clinical Cancer Research,* **20,** 5888-5897.

14.Rafferty, J, Farr, L, James, T, Chase, D, Heinrich, J, Brady, M (2016) A new magnetic resonance-based technique for high-resolution quantification of amorphous and quasi-amorphous structures. *Journal of The Royal Society Interface,* **13,**

15.Rajkumar, SV, Dimopoulos, MA, Palumbo, A, Blade, J, Merlini, G, Mateos, MV *et al* (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol,* **15,** e538-548.

16.Vasikaran, S, Cooper, C, Eastell, R, Griesmacher, A, Morris, HA, Trenti, T *et al* (2011) International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine Position on bone marker standards in osteoporosis. *Clin Chem Lab Med,* 10.1515/cclm.2011.602

17. APPENDICES:

17.1. APPENDIX A: Schedule of assessments

Type of Assessments	Time of Assessments	
	Baseline	6 months (or clinical relapse/progression)
Clinical history & Examination (Routine assessment)	X	X
Bloods and urine biomarkers *	X	X
Experimental MRI protocol	X	X*
DXA */** (Lumbar Spine and Hip Whole Body and VFA)	X	X
Quality of Life Questionnaire (EQ-5D) *	X	X
DWMRI/DXA Patient Experience Questionnaire *	X	X

*Not in healthy volunteers

**If participants have already had a DXA scan at OUH NHS Foundation Trust within 2 months of the visit date then we will use that scan and not repeat the scan for that site.

All procedures will happen during haematology clinic visit except DXA and MRI scan, which will be arranged for separate appointments.

17.2. APPENDIX B: MRI SAFETY CHECKLIST

See attached document <screening-form-volunteer-nov-2015.pdf>

University of Oxford
Centre for Clinical Magnetic Resonance Research
OCMR

VOLUNTEER MRI SAFETY SCREENING FORM

Please complete both sides

Volunteer name: _____

Date of birth: _____ **Weight:** _____ **kg** **Height**: _____ **m**

Please carefully check the following. Some items can interfere with MR examinations, and may be hazardous to your safety. Your answers will be kept strictly confidential. **Clearly mark your answer with a circle.**

IF YOU HAVE ANY QUESTIONS THEN PLEASE ASK US BEFORE YOUR SCAN		
Do you have a heart pacemaker or pacing wires?	YES	NO
Have you had any heart surgery?	YES	NO
Have you had any surgery to your head (including eyes/ears/brain), neck or spine?	YES	NO
Do you have any implanted devices (e.g. programmable hydrocephalus shunt, nerve stimulator, cochlea implant, aneurysm clip)?	YES	NO
Have you had any operation involving metallic pins / plates / screws / wires?	YES	NO
Have you ever had any other surgical procedure of any kind or gastroscopy including capsule endoscopy (PillCam ®)	YES	NO
Have you **ever** sustained any injuries involving metal to the eyes or any other part of the body?	YES	NO
Have you ever had a serious accident (e.g. road traffic accident, explosion injury, shooting, shrapnel injury?)	YES	NO
Have you ever had a fit or blackout, or do you suffer from epilepsy or diabetes?	YES	NO
Do you have any of the following (if yes please circle): Body/dermal piercing/jewellery — Hearing aid — Tattoos Dentures, dental implants — Skin patches (nicotine, pain, contraceptive, HRT, nitro) — Artificial limbs, prosthesis, splints or supports		
FOR WOMEN OF CHILDBEARING AGE: Do you have an IUD (coil)?	YES	NO
FOR WOMEN OF CHILDBEARING AGE: Could you be pregnant?	YES	NO
Have you removed your watch, spectacles, hearing aids, keys, coins, jewellery, hair grips?	YES	NO
Are you wearing any clothing that contains metallic threads or is “anti-microbial”?	YES	NO
Do you understand that this is a research scan and is not useful for diagnosis?	YES	NO

NO METAL OBJECTS TO BE TAKEN INTO THE MAGNET ROOM

Volunteer /Guardian signature_____ Date of study:_____

For admin use
Screened by *Signature:* *Print name:*

Version: November 2015 *Date of Next Review: November 2017*

For scans using contrast agent only: *(please ask a member of staff if you don't know whether your scan will involve contrast agent)*		
Have you had MR contrast agent before? (please leave blank if unknown)	YES	NO
Are you aware of any problems with your kidneys?	YES	NO
Do you have any allergies to medications? If yes please give details	YES	NO
Are you currently breast-feeding?	YES	NO

Notes (for staff use only) **- 1.5T / 3T (please circle magnet used)**

Heart rate:

Rhythm:

Scanned by:

The patient has been advised to let staff know if they experience any discomfort or heating during the scan due to the presence of tattoos/non-removable jewellery/piercing/implant

Yes / No / NA

Signature (Member of staff):

Signature (Volunteer):

Date:

Contrast	
Contrast name	
Dose/volume	
Batch number	
Expiry date	
Time of administration	
Given by	
Creatinine-Date	
eGFR	
Adenosine : batch number and expiry date	
Regadenoson: batch number / expiry date	

Version: November 2015 *Date of Next Review: November 2017*